SYNTHESIS OF 6-HYDROXY PIPERONYLIC ACID AND SOME RELATED COMPOUNDS

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DISSERTATION

Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in the Faculty of Pure Science of Columbia University.

BY

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ABSTRACT

This investigation was undertaken with the object of extending further the chemistry of the ortho hydroxy acids of the general type of salicylic acid and aspirin. These latter compounds, as is well known, have an extended use in medicine and particularly for their specific action in the case of rheumatic fever. Certain naturally occurring products such as piperonal, safrole and some of the alkaloids have a methlenedioxy group and hence the preparation of 6-hydroxy piperonylic acid and its acetyl derivative presents considerable interest both with regard to the relation of chemical constitution to pysiological properties and as to the presence of the specific action as is found in salicylic acid and aspirin.

Piperonal, which is commercially obtainable, was the starting material and the general plan was to proceed thru piperonylic acid on the one hand and thru nitro piperonal on the other.

The first course was found to be the more fruitful. Previous workers had prepared 6-amino piperonylic ester and this we converted to the hydroxy compound. The conversion took place with some difficulty. Acetylation of the hydroxy derivatives was found to be incomplete but especially so in the case of 6-hydroxy piperonylic acid. The corresponding reactions in the case of salicylic acid seem to take place easily and smoothly. Unfortunately the hydroxy piperonylic acid and its acetyl derivative were obtained in too small quantity to carry out physiological tests. In contra-distinction to methyl salicylate, 6-hydroxy methyl piperonylate has practically no odor.

Though 6-amino piperonal has already been obtained by an indirect process from 6-nitro piperonal, its production by direct reduction, a process unsuccessfully attempted by several previous investigators, has been shown to take place smoothly under the proper conditions.

It was also found that the condensation of nitro piperonal with ethyl urethane lead to excessive decomposition and that

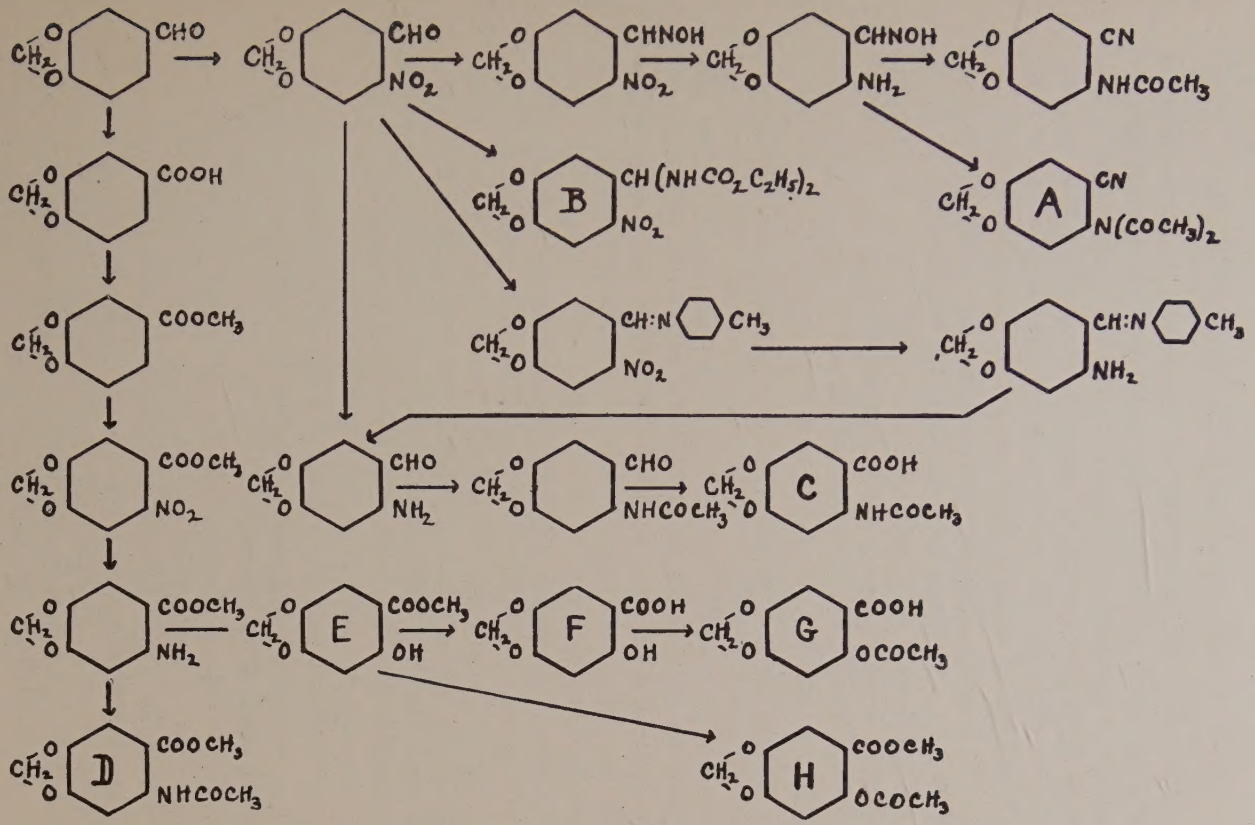
amino piperonal oxime gave to a large extent diacetyl piperonyl nitrile rather than acetamino piperonyl nitrile as described in the literature.

In the preparation of some of the intermediate products slight changes in conditions gave better yields.

The following new compounds were prepared in the course of the work:

[A] 6-diacetyl amino piperonyl nitrile.
[B] 6-nitro piperonal bis-urethane.
[C] 6-acetamino piperonylic acid.
[D] 6-acetamino piperonylic methyl ester.
[E] 6-hydroxy piperonylic methyl ester.
[F] 6-hydroxy piperonylic acid.
[G] 6-acetyl hydroxy piperonylic acid.
[H] 6-acetyl hydroxy piperonylic methyl ester.

Flow Sheet



Compounds indicated by capitals are new.

INTRODUCTORY AND HISTORICAL

In 1869, Fittig and Mielck[1] first described piperonylic acid and piperonal which they obtained by the oxidation of piperinic acid with permanganate solution. They also oxidized the piperonal thus obtained to piperonylic acid with warm permanganate solution. Its constitution as the 3, 4 methylene-ether of protocatechuic acid was shown by Fittig and Remsen.[2]

Piperonylic acid has also been prepared by oxidation of Safrole[4, 5] and the latter is the commerical source of piperonal.

Decker and Koch[11] described the preparation of piperonyl alcohol from piperonal by use of warm alcoholic potassium hydroxide solution. The by-product of this compensating oxidation and reduction is potassium piperonylate.

The oxidation of piperonal with potassium permanganate has been carried out by us in alkaline solution with an average yield of 60 to 70%, in neutral solution, using magnesium sulphate to maintain neutrality, with a yield of 45%, and also in acetone solution with a yield of 70%. Since the use of acetone solution gave no better yield than aqueous solution the latter was ordinarily used.

From piperonylic acid, Oertley and Pictet[16] prepared the methyl ester, nitrated this to 6-nitro piperonylic ester with fuming nitric acid at 0°C and then reduced the nitro compound to amino with stannous chloride. They converted the amino ester by means of the diazo reaction to hydrastic acid, which is known to be 3,4 methylene dioxy-o-phthalic acid and thus located the nitro group in the 6 position.

We have repeated the work of Oertley and Pictet as far as the preparation of 6-amino piperonylic methyl ester and with results as described by them.

The 6-amino piperonylic ester yielded an acetyl derivative by the usual method.

Attempts to replace the amino group by hydroxyl from diazotized 6-amino piperonylic methyl ester by warming with water, by steam distillation or by dropping the diazotized ester into boiling borax solution all failed, since the dark red product resulting resisted all attempts to purify it. A yield of 50%

was finally obtained by allowing the diazotized ester solution to drop into a boiling solution of copper sulphate. The reaction product was a mixture of 6-hydroxy piperonylic methyl ester and 6-hydroxy piperonylic acid, which were separated by appropriate means. The ester very largely predominated and it was found to have only a very faint pleasant odor even in solution.

From the purified ester, the 6-acetyl hydroxy piperonylic methyl ester was prepared in 60% yield by the usual means.

Hydrolysis of 6-hydroxy piperonylic methyl ester with boiling caustic alkali solution gave the corresponding acid with 80% yield. Both this acid and its methyl ester gave a beautiful deep blue coloration with ferric chloride solution. Salicylic acid and its ester give a deep violet coloration with this reagent.

Acetylation of 6-hydroxy piperonylic acid was very disappointing and succeeded very poorly. It was only after repeated fractional crystallizations of combined reaction mixtures from acetic anhydride that a small amount of this product could be obtained. The acid and its acetyl derivative seem to have about the same solubility in all the solvents tried, and the solubility was either very great or very slight. While the acetylation reaction was no doubt far from complete, the separation of the products offered the greater difficulty.

Nitro piperonal was also obtained in 1871 by Fittig and Remsen.[2] Concentrated nitric acid acted on piperonal only slowly in the cold but on slight warming a heavy red oil resulted which after steam distillation and recrystallization of the residue gave nitro piperonal.

Francis[12] showed that a small amount of nitro piperonal was obtained by nitrating piperonal with benzoyl nitrate.

Piperonal in common with certain other aldehydes of similar type yields both nitro aldehyde and a product in which the nitro group replaces the aldehyde group as has been shown by Salway.[13] Thus piperonal on nitration with concentrated nitric acid at O°C gave a mixture of nitro piperonal identical with that of Fittig and Remsen[2] and 4 nitro, 1, 2, methylene dioxy benzene, which had been described by Jobst and Hesse.[3] The nitro piperonal predominates about two to one.

Wilkendorf[21] has modified Salway's process by first dissolving the piperonal in glacial acetic acid which makes the process easier to carry out.

We have prepared considerable quantities of nitro piperonal by a slight modification of Salway's process which lead to a greater yield.

From a study of nitro piperonal and its oxidation product nitro piperonylic acid, Mameli[14] has shown that the nitro group enters in the 6 position.

Ciamician and Silber[9] have shown that the bright yellow compound produced when nitro piperonal is exposed to light is nitroso piperonylic acid.

The reduction of 6-nitro piperonal to 6-amino piperonal has been attempted by several previous investigators. Haber,[6] without giving details of methods tried, mentioned the failure of direct reduction. Friedlander and Schreiber[7] obtained 3, 4 methylene dioxy anthranil by reduction with tin and glacial acetic acid. Oertley[15] tried the reduction method of Tiemann and Oppermann but did not succeed. We were unsuccessful using the Bamberger method which is used in the preparation of o-amino benzaldehyde from o-nitro benzaldehyde,[8] by the use of titanous chloride,[10] or by the use of hydrogen sulphide and ammonia.

In 1913, Rilliet and Kreitmann,[17] after reviewing the failures of the other workers, succeeded in obtaining 6-amino piperonal by an indirect process. Nitro piperonal was condensed with p-toluidine, a reaction easily carried out and giving a good yield. The resulting 6-nitro piperonylidene p-toluidine was reduced by sodium sulphide in alcohol solution to the amino compound which upon hydrolysis gave 6-amino piperonal.

Repetition of this work by us has shown that a 20% excess of p-toluidine in the condensation reaction gave a considerably increased yield of product. Our 6-amino piperonylidene p-toluidine had a somewhat higher melting point than that given by Rilliet and Kreitmann. Analysis however showed that the products were identical.

We also tried the reduction method suggested by Cobenzl,[19] namely sulphur and sodium sulphide in alcohol solution. While 6-amino piperonylidene p-toluidine was obtained the yield was 10% or 15% less than with sodium sulphide alone.

Rilliet and Kreitmann stated that they hydrolysed the 6-amino piperonylidene p-toluidine by boiling with dilute sodium hydroxide. We however could get no hydrolysis even by a steam distillation in 10% sodium hydroxide continued for two days. It was found that if 5% alcoholic potassium hydroxide were used instead of aqueous alkali, hydrolysis took place readily.

The direct reduction of 6 nitro piperonal with a 60% yield was finally accomplished by us using ferrous sulphate and ammonia according to the method described by Jacobs and Heidelberger.[20] The 6-amino piperonal and its acetyl derivative were identical with the products described by Rilliet and Kreitmann.

Oxidation of 6 acetamino piperonal with permanganate solution kept neutral by magnesium sulphate gave us 6 acetamino piperonylic acid.

Attempts to replace the amino group by hydroxyl from diazotized 6-amino piperonal, either by boiling with water or by dropping the diazotized solution into boiling copper sulphate solution gave a dark red product which could not be purified.

In 1913 Bianchi[18] condensed piperonal with ethyl urethane and obtained a product easily hydrolysed and in good yield. We hoped that a similar condensation product from nitro piperonal, after reduction, might lead to amino piperonal. When the reaction was carried out it was found that excessive carbonization and tar formation took place. The product was difficult to purify and the yield less than 10% of theory. This condensation product was light and feathery also very triboelectric and hence difficult to handle when dry. Since the yield was so poor no further work was done in this direction.

Haber[6] described 6-nitro piperonal oxime but gave no details as to conditions or yield. We found that dry potassium carbonate gave better results as a condensing agent than zinc oxide in preparing this oxime from nitro piperonal and hydroxylamine hydrochloride.

Reduction of this product with hydrogen sulphide in amoniacal alcohol solution gave Haber 6-amino piperonal oxime. We also obtained this product in the same way but our melting point was about 7° higher than his.

By heating 6-amino piperonal oxime with an excess of acetic anhydride and sodium acetate for a short time, Haber obtained 6 acetamino piperonyl nitrile for which he gave the melting point as 213°. All the directions given by Haber are contained in the above. When we first carried out this reaction the mixture was heated for an hour but the product obtained, after purification melted at 146°-147° and there was no evidence of any higher melting product. Analysis of this compound checked fairly well with a diacetyl piperonyl nitrile. Since Haber had stated that the 6-amino piperonyl nitrile did not condense to an indazole the possibility of this type of product seemed to be ruled out.

Evidently heating the mixture for an hour carried the reaction too far, so heating for shorter periods was tried. When the time was limited to 10 or 12 minutes a small amount of product of m.p. 215°-217° was isolated and this upon analysis gave figures which checked for an acetamino piperonyl nitrile. Shorter periods of heating gave no result, nor did reaction take place when carried out in boiling solvents such as ethyl acetate or isoamyl acetate, the amino oxime being recovered unchanged.

EXPERIMENTAL

Piperonylic Acid.

Fifty grams of piperonal were finely powdered and added to 3 liters of water and heated to 40°-50° C. Potassium permanganate solution was allowed to drop in slowly with constant mechanical stirring until the odor of piperonal disappeared. This required about 125 grams of $KMnO_4$. The excess of $KMnO_4$ if any, was reduced with alcohol and the precipitated MnO_2 filtered and washed by suction. The solution was acidified by HCl and cooled, the piperonylic acid filtered off, washed and dried. Yield 36 grams or 65% of theory.

Piperonylic Acid Methyl Ester.

Cf. Oertely and Pictet.[16]

Fifty grams of piperonylic acid and 500 grams of acetone free methyl alcohol were heated to boiling under reflux condenser and dry HCl gas passed in until saturated. The mixture was then cooled and HCl gas was again passed in until saturated. The mixture was then heated to boiling under reflux condenser and dry HCl gas passed in until all the piperonylic acid was dissolved. The solution was poured into a large volume of ice water and the white precipitate filtered off, washed and dried. When recrystallized from dilute methyl alcohol it melted at 52°-53°. Yield 49 grams or 90% of theory. Oertley and Pictet gave m.p. 53°.

6-Nitro Piperonylic Methyl Ester.

Cf. Oertley and Pictet.[16]

To a mixture of 50 c.c. glacial acetic acid and 100 c.c. of fuming HNO_3 (Sp. Gr. 1.50) cooled to 10° C. was added 20 grams of methyl piperonylate in small portions such that the temperature remained below 10°C. The solution was allowed to stand 15 to 30 minutes after all the ester had been added and then poured into ice water. The precipitate was filtered off, washed and bone blacked in alcohol solution. On cooling the alcoholic filtrate deposited small, nearly white needles, which turned yellow on exposure to light. M.p. 102°.6-103°.6. Yield 23 grams or 88% theory. Oertley and Pictet gave m.p. 102°.

6-Amino Piperonylic Methyl Ester.

Cf. Oertely and Pictet.[16]

A mixture of 400 c.c. glacial acetic acid and 140 grams of $SnCl_2$ was satured with dry HCl gas, when practically all the $SnCl_2$ dissolved. 40 grams 6-nitro methyl piperonylate were added in small portions with constant shaking, the solution warmed up and turned slightly yellow. The flask was kept at such a temperature that it could be comfortably held in the hands. After about half the nitro ester had been added a white precipitate began to separate. The mixture was allowed to cool down and stand over night. The next day it was warmed

to 50°-60° on the water bath for 1 to 2 hours and again allowed to stand over night. The white precipitate was filtered off and added to ice and a small amount of water, made alkaline with NaOH solution at O°C., and the solution then extracted several times with ether. The ethereal solution was dried over $CaCl_2$ and the ether distilled off. Yield 20 grams or 60% of theory. Recrystallized from dilute alcohol it formed white needles m.p. 107°.8-108°.8. The m.p. given by Oertley and Pictet was 108°.

6-Acetamino Piperonylic Methyl Ester.

Five grams of 6-amino piperonylic methyl ester were dissolved in 100 c.c. glacial acetic acid and an excess of acetic anhydride added. The mixture was heated 1/2 hour and poured into cold dilute sodium carbonate solution. The precipitate was filtered, washed with water and recrystallized from alcohol. It formed white fine fluffy needles m.p. 183°-184°. Yield 6 grams or 95% of theory. Soluble in alcohol, benzol, acetone, chloroform, slightly soluble in ether, very difficultly soluble in water. Dried in vacuo over sulfuric acid for several hours and analysed.

Analysis

0.1055 grams gave 0.0456 grams H_2O and 0.2157 grams CO_2.
0.1124 grams gave 0.0507 grams H_2O and 0.2303 grams CO_2.
Found C 55.63%, 55.88%, H 4.83%, 4.93%
Calculated for $C_{11}H_{11}O_5N$ C 55.70%, H 4.64%

6-Hydroxy Piperonylic Methyl Ester.

Five grams of 6-amino piperonylic methyl ester were dissolved in the warm solution of 10 grams sulfuric acid in 25 c.c. of water and the solution cooled. The calculated quantity (2.15 grams) of potassium nitrite was dissolved in 10 c.c. of water and added to the ester solution with cooling. The diazotized solution was then allowed to drop slowly from a dropping funnel into a boiling solution of 25 grams copper sulfate in 25 c.c. water. Gas was evolved and a very small amount of

white product distilled with the steam (the reaction flask was connected to a Liebig condenser to catch any volatile product). After all the diazotized solution was added the mixture was poured into 400-500 c.c. of water and allowed to stand over night. A reddish brown precipitate separated which was filtered off, washed with water to free from copper sulfate and boneblacked in alcohol solution. On cooling white rosettes m.p. 97°-98° separated. Yield about 50% of theory.

This product was found to be a mixture and was separated as follows: It was first shaken with dilute sodium carbonate solution and filtered. On acidification of the filtrate a small amount of nearly white precipitate formed. The residue from the sodium carbonate treatment was then shaken with dilute NaOH solution when the greater part dissolved if the NaOH was not too concentrated. In the latter case a white precipitate was formed.

On acidification of the NaOH solution a nearly white precipitate formed, which was filtered, washed and dried and then dissolved in a mixture of alcohol and ether in which it was very soluble and then allowed to crystallize by evaporation. The 6-hydroxy piperonylic methyl ester crystallized in small white rosettes m.p. 99°-100°. With ferric chloride solution it gave a beautiful deep blue coloration. The ester has practically no odor. It was dried over sulfuric acid in vacuo for several hours and analysed.

Analysis

0.1016 grams gave 0.0388 grams H_2O and 0.2056 grams CO_2.

Found	C 55.19%	H 4.28%
Calculated for $C_9H_8O_5$	C 55.10%	H 4.11%

6-Acetyl Hydroxy Piperonylic Methyl Ester.

Five grams of 6-hydroxy piperonylic methyl ester were heated 2 or 3 hours under reflux condenser with a considerable excess of acetyl chloride. The mixture was then poured into dilute sodium carbonate and filtered. After drying the precipitate was dissolved in ether and boneblacked. Nearly white

crystals separated m.p. 50°-60°. The product was then recrystallized from a mixture of alcohol and ether. Nearly white rosettes of needles separated m.p. 97°-98°, yield 3.5 grams or 60% of theory. After drying for several hours over sulfuric acid in vacuo it was analysed.

Analysis

0.1227 grams gave 0.0466 grams H_2O and 0.2488 grams CO_2.

Found	C 55.29%	H 4.25%
Calculated for $C_{11}H_{11}O_6$	C 55.46%	H 4.20%

6-Hydroxy Piperonylic Acid.

Ten grams crude 6-hydroxy piperonylic methyl ester were dissolved in hot alcohol, boneblacked, filtered and allowed to crystallize. The resulting product which was still somewhat reddish brown in color was dissolved in cold 5% KOH solution filtered and the filtrate saturated with carbon dioxide. The precipitate was slightly brown in color while the solution was dark reddish brown. The precipitate was filtered off and dissolved again in 5% KOH solution and boiled until a test portion gave no precipitate with carbon dioxide. This required about an hour. The solution had a slight reddish color. It was acidified by dilute HCl, filtered, washed and dried. Yield 7 grams or 80% of theory.

A small amount was recrystallized from a large volume of chloroform in which it was difficultly soluble. On cooling and spontaneous evaporation of the solvent, nearly white fluffy needles separated m.p. 211°-212°. Recrystallization of a small portion from dilute alcohol gave the same product. Difficultly soluble in water chloroform, ether and benzol. Very soluble in alcohol. Dried in vacuo over sulfuric acid for several hours.

Analysis—Product from Alcohol

0.1044 grams gave 0.0304 grams H_2O and 0.2005 grams CO_2.

Found	C 52.38%	H 3.24%

Analysis—Product from chloroform

0.1200 grams gave 0.0352 grams H_2O and 0.2308 grams CO_2.

Found	C 52.45%	H 3.26%
Calculated for $C_8H_6O_5$	C 52.74%	H 3.29%

6-Acetyl Hydroxy Piperonylic Acid.

An exact method of procedure for obtaining this compound is difficult to give since no acetylation method tried gave any appreciable yield. It was only by working over the results of several apparently unsuccessful attempts that sufficient product was obtained to get analyses and save a small sample.

About equal parts of 6-hydroxy piperonylic acid and fused sodium acetate were dissolved in acetic anhydride and an excess of acetyl chloride added. The mixture was boiled for 6 to 8 hours and allowed to cool and then poured into a considerable volume of cold water and the precipitate filtered, washed and dried. Fractional crystallization of this product from acetic anhydride repeated 5 or 6 times, washing the crystals with a little cold ether each time, finally yielded a small amount of nearly white needles m.p. 155°.5-156°.5 with slight preliminary softening. Apparently 6-hydroxy piperonylic acid and its acetyl derivative have approximately the same solubility in the ordinary solvents. Very soluble in alcohol, glacial acetic acid or acetic anhydride. Very difficultly soluble in water, chloroform, benzol or ether.

Analysis

0.0779 grams gave 0.0278 grams H_2O and 0.1536 grams CO_2.

Found	C 53.77%	H 3.96%
Calculated for $C_{10}H_8O_6$	C 53.57%	H 3.57%

6-Nitro Piperonal.

Cf. Salway.[13]

Five hundred c.c. of concentrated nitric acid (Sp. Gr. 1.42) were cooled in ice salt mixture to O°C. and then 50 grams of finely powdered piperonal added in small portions with constant mechanical stirring, the temperature being kept below O°C.

If after 2 or 3 hours the piperonal was not entirely dissolved the freezing mixture was removed and the solution allowed to warm up. As soon as complete solution took place the mixture was poured into ice water. A light yellow precipitate separated which was filtered off, washed to remove nitric acid. The product was then stirred with sufficient 40% sodium bisulphite solution to give a thick paste. About two volumes of water were then added and the mixture filtered. The residue was then submitted to the same treatment 3 or 4 times. The combined filtrates were made alkaline with sodium hydroxide, the precipitate filtered by suction and washed with water to remove the alkali. The nitro piperonal was crystallized from a 50% mixture of ethyl alcohol and ethyl acetate giving long, slightly yellow needles m.p. 97°-98°. Yield 46 grams or 70% of theory, together with 14 grams of 6-nitro 1, 2-methylenedioxy benzene, which accounts for 96% of the piperonal used. Salway gave the m.p. 98°.

6-Nitro Piperonal Bis-Urethane.

Five grams of 6-nitro piperonal and 4.86 grams of ethyl urethane were heated in an oil bath maintained at 100°-110°C. to a clear yellowish liquid. When fusion was complete 1 c.c. conc. HCl was added and the mixture stirred. The heating was continued until vapor ceased to be evolved. When the HCl was added the mixture turned green and then rapidly began to turn brown until finally it was almost black and became solid. The product was allowed to stand over night, then dissolved in a mixture of alcohol, chloroform and acetone, boneblacked for several hours and filtered. Upon cooling and concentration of the filtrate a slightly brownish product separated. This was filtered off from the dark brown solution washed with a little cold alcohol and then boneblacked again in ethyl acetate solution. On cooling a fine feathery, nearly white product separated. It had a slight yellowish green tinge, which turned to a yellow brown color on long exposure to light. Yield 1 gram or 10% of theory, m.p. 207°-208° with decomposition.

Analysis of sample dried in oven at 110°-115°*C*

0.1077 grams gave 0.0506 grams H_2O and 0.1853 grams CO_2.
0.1034 grams gave 0.0456 grams H_2O and 0.1769 grams CO_2.
0.1143 grams gave 12.1 c.c. N_2 at 767 mm. and 23°.5C.

Found	C 47.10%	H 5.27%	N 11.98%
	C 46.67%	H 4.94%	
Calculated for $C_{14}H_{17}O_8N_3$	C 47.32%	H 4.83%	N 11.83%

The reaction mixture was very hard to purify since it was very soluble or very insoluble in all ordinary solvents or mixtures of solvents. Soluble in both acid and alkali. The purified product was very light and fluffy and extremely tribo-electric, which made it difficult to handle since it flew all over when touched with a spatula.

6-Nitro Piperonylidene P-Toluidine.

Cf. Rilliet and Kreitmann.[17]

Twenty-six grams of 6-nitro piperonal and 17 grams of p-toluidine (120% of theory) were heated together in an oil bath at 120°-130°C. for 4 hours. The resulting product was cooled, pulverized and recrystallized from boiling alcohol. Since the condensation product is very sensitive towards light, turning to a dark red color, these operations were carried out as far as possible in the dark. Long yellow needles from alcohol m.p. 121°-122°. Yield 34.5 grams or 90% of theory. Recrystallized from ether and ethyl acetate in long glistening yellow needles m.p. 121°-122°. Rilliet and Kreitmann give the yield as 75% of theory and m.p. 121°.5.

6-Amino Piperonylidene P-Toluidine.

Cf. Rilliet and Kreitmann.[17]

Ten grams of nitro piperonylidene p-toluidine were dissolved in boiling alcohol and to this was added a solution of 15 grams sodium sulfide crystals dissolved in dilute alcohol, the mixture being kept boiling to prevent precipitation. The solution was then placed in an ice salt mixture and on cooling small yellow plates separated and the solution became a dark reddish

brown. The precipitate was filtered off, washed with cold alcohol and then with water until the washings were colorless. Yield 5 grams or 60% of theory. The product was recrystallized twice from alcohol and once from benzol in which it is very soluble. On cooling and evaporation 1 gram of small rosettes of fine silky yellow needles separated m.p. 137°-138°. Rilliet and Kreitmann gave the yield as 54% and the melting point as 134°.5. When dried over sulfuric acid in vacuo for several hours it was analysed.

Analysis

0.1046 grams gave 0.0547 grams H_2O and 0.2708 grams CO_2.
0.1006 grams gave 9.6 c.c. N_2 at 766 mm. and 22°C.

Found	C 70.61%	H 5.85%	N 10.89%
Calculated for $C_{15}H_{14}O_2N_2$	C 70.82%	H 5.60%	N 11.02%

6-Amino Piperonal.

(*Hydrolysis of 6-amino piperonylidene p-toluidine*).

After repeated attempts to hydrolyse 6-amino piperonylidene p-toluidine by boiling with dilute sodium hydroxide using 5% and 10% solution and even continuing the process for 16 to 20 hours with no result the following proceedure was adopted.

Six grams of 6-amino piperonylidene p-toluidine was added to the solution of 15 grams of KOH in 300 c.c. of alcohol and boiled under reflux condenser for 3 or 4 hours. Then about an equal volume of water was added and the mixture subjected to steam distillation until no more p-toluidine came over. The residue in the flask was filtered hot and allowed to cool. Brownish yellow needles separated which were recrystallized from hot water. M.p. 107°-108°. Yield about 50%. Rilliet and Kreitmann gave the m.p. 107°.

6-Amino Piperonal.

(*Direct reduction of nitro piperonal*).

One hundred grams of ferrous sulfate were dissolved in 500 c.c. of boiling water and 10 grams nitro piperonal dissolved in hot water added. To this was added in small portions with constant shaking about 100 c.c. conc. ammonia until the solu-

tion was alkaline to litmus. Boiled 5 minutes and filtered with suction washing the residue on the funnel thoroly with boiling water. On cooling the filtrate a yellow solid separated, which was recrystallized from hot water and gave long yellow needles m.p. 107°-108°. Yield 5 grams or 60% of theory. The product was identical with that prepared by the method of Rilliet and Kreitmann.

6-Acetamino Piperonal.

Cf. Rilliet and Kreitman.[17]

Five grams 6-amino piperonal were dissolved in 100 c.c. of glacial acetic acid and a slight excess of acetic anhydride added and the solution heated to oiling for 10 or 15 minutes. Fine white needles separated on cooling which were recrystallized from water in fine white needles m.p. 161°-162°. Yield 4.5 grams or 75% of theory. Rilliet and Kreitman gave m.p. 160°.

6-Acetamino Piperonylic Acid.

Three grams of 6-acetamino piperonal were dissolved in 300 c.c. of hot water, sufficient$MgSO_4$ added to keep the solution neutral and then $KMnO_4$ solution added slowly until a slight color persisted for 2 or 3 minutes. A small amount of alcohol was added to reduce excess of permanganate and the solution filtered. After cooling the filtrate was acidified with dil. H_2SO_4 and the precipitate filtered off, washed and dried. It crystallized from dilute alcohol in nearly white (slightly yellowish) long feathery needles m.p. 124°-125°. Yield 0.4 gram. Difficultly soluble in water, soluble in alcohol. Dried in vacuo over H_2SO_4 and analysed.

Analysis

0.1036 grams gave 0.0382 grams H_2O and 0.2012 grams CO_2.
0.0528 grams gave 0.0229 grams H_2O and 0.1048 grams CO_2.
Found C52.97%,54.13%,H4.09%,4.81%
Calculated for $C_{10}H_9O_5N$ C 53.81% H 4.03%

While these analyses are not very satisfactory the method of preparation seemed to leave no doubt as to the identity of the compound. Lack of material prevented repeating the analysis.

6-Nitro Piperonal Oxime.

Cf. Haber.[6]

Ten grams of 6-nitro piperonal and 3.6 grams of hydroxylamine hydrochloride were dissolved in alcohol and 3.6 grams of dry K_2CO_3 dissolved in a little water were added. This mixture was boiled on the water bath for 3 hours and on cooling a yellow product separated. Recrystallized from alcohol it formed a yellow powder m.p. 201°-203°. Yield 9 grams or 84% of theory. Haber described this compound as yellow needles m.p. 203°.

6-Amino Piperonal Oxime.

Cf. Haber.[6]

Ten grams of nitro piperonal oxime were suspended in 125 c.c. of conc. NH_4OH and an equal volume of alcohol added. H_2S was then passed into the mixture while being warmed on the water bath under reflux condenser. When complete solution took place which usually required 1½ to 2 hours, the mixture was poured into an equal volume of water and allowed to cool. The product was filtered and washed, then dissolved in hot alcohol and bone blacked. Nearly white, glistening needles separated m.p. 182°-183°. Yield 7 grams or 81% of theory. Haber gave the m.p. as 175°.5.

6-Diacetyl Amino Piperonyl Nitrile and 6-Acetamino Piperonyl Nitrile.

Two and a half grams of 6-amino piperonal oxime, 2 grams of fused sodium acetate and 15 grams of acetic anhydride were heated together for 1 hour and the mixture then poured into cold dilute Na_2CO_3 solution, filtered, washed and dried. The product was dissolved in boiling alcohol and on cooling thin rectangular plates separated. Yield 1.5 grams m.p. 115°-122°. This result was wholly unexpected as Haber gave the m.p. of 6-acetamino piperonyl nitrile as 216°. The product was dissolved in chloroform in which it is exceedingly soluble (10 c.c. dissolved 1.5 grams in the cold). Upon spontaneous evaporation, thin colorless rectangualr plates separated, m.p. 146°-147°. These were dried in vacuo over H_2SO_4 and analysed.

Analysis

0.1100 grams gave 0.0410 grams H_2O and 0.2365 grams CO_2.
0.1195 grams gave 12,6 c.c. N_2 at 766 mm. and 23°C.
0.1085 grams gave 11.6 c.c. N_2 at 765 mm. and 25°C.
Found C 58.64% H 4.18% N 11.92, 11.93%.
Calculated for $C_{12}H_{10}O_4N_2$ C 58.54% H 4.07% N 11.38%

The product is thus a diacetyl piperonyl nitrile in all probability, since the analytical figures agree fairly well with the calculated values for this compound.

This being the case the reaction was evidently carried too far and a shorter heating should give the compound described by Haber.

Two grams of 6-amino piperonal oxime, 1 gram of fused sodium acetate and 20 grams of acetic anhydride were heated together for 10 to 12 minutes and the reaction mixture poured into cold dilute Na_2CO_3 solution, filtered washed and dried. Yield 1 gram. When crystallized from alcohol the product was found to be a mixture of fine feathery needles m.p. 200°-210° and clear needles or plates m.p. 115°-122°. Consequently the mixture was dissolved in chloroform and on cooling a small amount (about 0.3 gram) of fine feathery needles separated m.p. 215°-217°. These were dried in vacuo over H_2SO_4 for several hours and analysed.

Analysis

0.1145 grams gave 0.0432 grams of H_2O and 0.2468 grams CO_2.
0.1017 grams gave 12.6 c.c. of N_2 at 764 mm. and 25°C.
Found C 58.78% H 4.22% N 13.82%
Calculated for $C_{10}H_8O_3N_2$ C58.82% H 3.92% N 13.73%

Haber gave as the m.p. 216°.

Shorter periods of heating did not seem to give any appreciable amount of this compound nor was the reaction found to take place in boiling ethyl acetate or isoamyl acetate solution, the amino oxime being recovered unchanged. The yield of the desired product was so small that it did not seem profitable to continue further in this direction.

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